Application No.: 09/743,746
Attorney Docket No.: 068800-0276611

REMARKS

I. Status of the claims

Claims 1-6, 8, 9-31, and 35-39 are pending. Applicants have amended claims 1, 5, 6, 8, 10, 12, 13, and 20. Support for the substantive amendments to claim 1 may be found on pages 11-12 of the specification and in original claims 7 and 9.

II. Written Description Rejection

The examiner has rejected claims 1, 2, 4-6, 8, 10-12, 20-22, and 31 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Applicants traverse this rejection.

The examiner bases this rejection, at least in part, on the lack of representative examples in Applicants' specification. Citing *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1545 (Fed. Cir. 1997), the examiner states that "adequate disclosure, like enablement, requires representative examples, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention." (emphasis added).

This a legally incorrect recitation of the law. After perusing *Eli Lilly* as well as *In re Riat*, both of which were cited by the examiner as supporting this statement, Applicants have been unable to find any language in either of those cases that could support such a statement. In fact, Applicants do not know of a single Federal Circuit or CCPA opinion that stands for the proposition that an applicant must provide representative examples of the invention to comply with the written description requirement.

Applicants submit that the examiner may be confusing MPEP section 2163, which states,

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

MPEP § 2163 (emphasis added). However, this passage, which the MPEP attributes to *Eli Lilly*, simply provides that a representative number of species may be sufficient to satisfy the

written description requirement; no requirement of a representative number of species or representative examples is ever stated.

Furthermore, the aspects of the claimed invention identified by the examiner as having too large a scope--the analyte, cleavable linker, and reporter elements--are all elements that were recited in both the original claims and the specification as filed. As the examiner should know, a description as filed is presumed to be adequate written description, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See *In re Marzocchi*, 439 F.2d 220 (CCPA 1971); *see also In re Wertheim*, 541 F.2d 257 (CCPA 1976) ("There is a strong presumption that an adequate written description of claimed is present when the application is filed."). There is absolutely no reason why the examiner should not apply that legal presumption to this application and the claimed invention.

The individual issues raised by the examiner under this written-description rejection, which Applicants submit relate to the enablement of the invention, are addressed by Applicants in section III of this response.

In view of the foregoing, Applicants respectfully request that the examiner withdraw the written description rejection under 35 U.S.C. § 112, first paragraph.

III. Enablement Rejection

The examiner has rejected claims 1-2, 4-12, 20-22, and 31-34 under 35 U.S.C. § 112, first paragraph as failing to be enabled by the specification. Applicants respectfully traverse this rejection.

Applicants discuss the enablement issues raised by the examiner below. Additionally, because the merits of the written description rejection set forth in this Office Action pertain to enablement issues, as discussed above, Applicants in this portion of the response address all substantive issues presented in paragraphs 7-10 (on pages 3-11) of the Office Action.

With respect to the examiner's rejection based on the lack of a specific analyte, the examiner acknowledges that proteins are supported/enabled as Applicants have demonstrated coupling reactions to nucleophiles in proteins, specifically amines and thiols. It is well known in the art that vinyl sulphones will, under appropriate conditions, react with hydroxyls and that this reaction can be reversed by beta elimination. It is submitted that oligonucleotides are also supported/enabled as it is trivial to introduce the sane nucleophiles

present in proteins into oligonucleotides, i.e. amines, thiols and hydroxyls. In this regard, claim 1 has been limited to biological molecules that comprise these three nucleophiles.

Claim 1 has also been amended to state that the cleavage takes place by beta elimination between the R' group and the adjacent carbon atom. This defines the actual mechanism of cleavage of all of the preferred linkages. Cleavage occurs between the R' group and the adjacent carbon atom in the beta position with respect to the sulphone or sulphoxide as shown in the figure below:

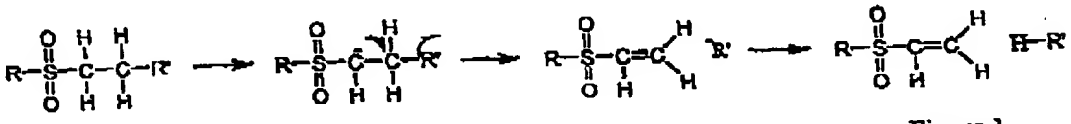

Figure 1

This amendment addresses the examiner's rejection based on the allegation that the cleavage could take place anywhere in the molecule irrespective of the nature of the linker that we are showing.

With regard to the examiner's repeated statement that only trifluoroacetyl and mesyl groups are supported/enabled, some clarification of the chemistry should address this objection. As shown in figure 1, the first step of a beta elimination reaction involves the abstraction of a proton from the molecule, which must localize (eventually) at the alpha carbon adjacent to the sulphone group (or sulphoxide). This proton abstraction can be caused by collision, i.e. during electrospray ionization, by thermal means or chemically through the use of appropriate basic reaction conditions. This leaves a negative charge at the alpha carbon that can then initiate the elimination, which results in a negative charge being left on the R' group. This charge can be stabilized, if this is desired, as long as the appropriate R' group is present, e.g. if R' is a suitable amide. The specification demonstrates that the trifluoroacetatamide and methylsulphonamide groups work well although it would be reasonable to expect a large variety of amides and sulphonamides to perform well. These two groups were chosen as they can be easily removed during later synthetic steps, but the tosylate group may also be used for this purpose. See the carry-over paragraph on pages 11 and 12 of the specification. If the negative charge on the R' group is stabilized then the final step shown in the figure, where the R' group is neutralized would not take place. This stabilization is not actually necessary but it is advantageous when the R' group is the reporter group as the cleavage leaves a negative charge on the reporter, which can be otherwise

uncharged. Applicants elected the trifluoroacetyl modified linkage for examination as it is preferred, not because it contains any essential features.

It is also theorized that a sulphoxide or sulphone at R' will stabilize a negative charge and facilitate a beta elimination reaction. This can occur if a vinyl sulphone is reacted with a free cysteine thiol on a protein, and the resultant thioether is then oxidized. This reaction is discussed in the last paragraph of page 13 of the specification.

However, if R' is an amine, thioether or ordinary ether linkage the negative charge on R' group would be rapidly neutralized after the beta elimination, particularly if the cleavage reaction took place in solution prior to mass spectrometry analysis of the cleaved tags. In solution, the negatively charged R' group would abstract a proton from the solvent, particularly as the protons removed from the alpha carbon will be available (on average) from the solvent. In a protein, which usually has many charged groups, both positive and negative, proton migration would also rapidly neutralize the charge. Applicants believe that this takes place when phenyl vinyl sulphone is cleaved thermally from cysteine thiol groups of a labeled protein. See the example in the second and third paragraphs on page 42 of the specification. This embodiment is advantageous when the R' group is not the reporter but the analyte.

Therefore, the examiner is incorrect in his assertion on page 10 that only a trifluoroacetyl group or methylsulphate group are supported/enabled in alleging that these are the only groups that can stabilize a negative charge. It is not necessary to stabilize the negative charge in all situations; this is an advantage where R' comprises the reporter group and a negative ion tag is desired. The negative charge will neutralize itself under most circumstances particularly if the cleavage reaction takes place in solution prior to mass spectrometry.

Applicants also respectfully submit that the examiner appears to have misunderstood the example on page 41 when referring to methyl sulphate as being required to stabilize a negative charge. See page 7 of the Office Action. The examiner is either referring to the methylsulphonamide group (sometimes called a mesyl group) or he has misunderstood the example on page 41. This example demonstrates that phenyl vinyl sulphone can be cleaved chemically from the lysine amino groups. In this reaction diniethyl sulpbate is a methylation reagent and the reaction described is shown in the following figure:

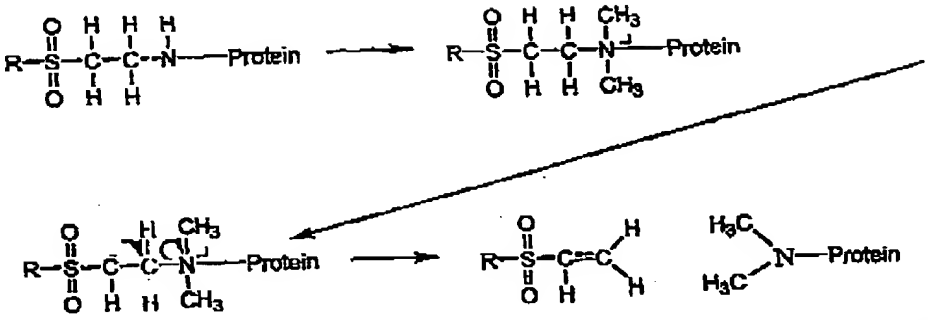

Figure 2

It can be seen in Figure 2 that a vinyl sulphone (Phenyl Vinyl Sulphone in the example on page 41 of the specification) has been reacted with lysine amino groups in a protein (albumin in the example). The resulting secondary amine is methylated in the first step (using dimethyl sulphate in the example) to give a quaternary ammonium ion. Addition of a base (diisopropylethylamine in the example) facilitates abstraction of a proton from the carbon in the alpha position of the ethyl sulphonyl linkage initiating the elimination reaction. In this case the negative charge that would normally end up at the R' position is now neutralized (not stabilized) by the presence of a positively charged quaternary ammonium group. In the example in the specification, the phenyl vinyl sulphone was then detected by Gas Chromatography Mass Spectrometry using electron impact ionization to generate a characteristic positive ion. Alternatively, electrospray ionization could be used if the R group was able to ionize (either in the positive or negative mode). Applicants also have data showing that thermal cleavage of phenyl vinyl sulphone can take place directly from an unmodified amine. Thus, the examiner's assertion that the negative charge needs to be stabilized is wholly incorrect.

Additionally, the examiner has stated that the disclosure of the invention does not provide sufficient support/enablement for one of ordinary skill in the art to reasonably expect that all of the possible choices of R and R' groups will be cleavable and will give rise to a detectable signal by mass spectrometry. In the response to the previous Office Action, Applicants limited R' to comprising a group selected from –S-, -SO-, -NR^1- , and –O- between the C atom that is in the β-position to the SO_n group, and the reporter group or analyte, wherein R' is a hydrogen atom, a halogen atom, or a substituent comprising a carbonyl group and/or a halogen atom. Claim 1, as amended, is structurally limited to the analyte comprising a biological molecule comprising a nucleophile selected from the group

consisting of amines, thiols and hydroxyls and limited to the cleavage taking place by beta elimination between the R' group and the adjacent carbon atom. It is submitted that the specified structural features of compounds specified in amended claim 1 would allow cleavage of the reporter group from the analyte by beta elimination, as discussed in detail above. It is also submitted that it would not require undue experimentation and that further examples are not required in order for the skilled person to perform the method according to new claim 1.

In view of the above and the amended scope of claim 1, it is submitted a sufficient number of examples have been provided in the specification to enable and support the claimed invention and that the scope of amended claim 1 is justified. Accordingly, Applicants respectfully request that the examiner withdraw the rejections based on 35 U.S.C. § 112, first paragraph.

IV. Rejection under 35 U.S.C. § 102(b)

The examiner has rejected claims 1, 2, 4-9, 11-12, 20, and 31-34 under 35 U.S.C. § 102(b) as being anticipated by the article authored by Nothnagel ("Nothnagel"). Applicants respectfully traverse this rejection.

As Applicants previously remarked, Nothangel discloses the synthesis of a probe molecule. This probe molecule is characterized by FAD mass spectrometry to confirm its identity. There is fragmentation of the probe as part of this characterization process. However, there is no indication that a specific cleavage took place to give rise to a characteristic reporter species that gives rise to a predetermined ion that could be used to identify an analyte. The examiner points out that the wording of claim 1 does not actually refer to a specific cleavage and is thus not limited to this. The examiner also points out that claim 1 refers to analytes being characterized, not identified.

In view of the examiner's comments, claim 1 has been amended to refer to a method to "identify an analyte" rather than to "characterize an analyte." Claim 1 has also been amended to define that the cleavage takes place by beta elimination between the R' group and the adjacent carbon atom.

As amended, claim 1 and its dependent claims are novel over Nothangel. Accordingly, Applicants respectfully request that the examiner withdraw this rejection under 35 U.S.C. § 102(b).

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V. Conclusion

If any issues in the prosecution of this application remain unresolved, the examiner is encouraged to contact the undersigned counsel at the number listed below in order to resolve such issues.

Please charge any fees associated with the submission of this paper to Deposit Account No. 033975. The Director is also authorized to credit any overpayments to the above-referenced Deposit Account.

Respectfully submitted,
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